Heart functional responses to pressure overload in exercised and sedentary rats

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Heart functional responses to pressure overload in exercised and sedentary rats. Am. J. Physiol. 230(1): 199-204. 1976. — Female rats that had been subjected to a moderate treadmill running program were compared with sedentary animals on the basis of heart weight, selected biochemical measurements, and heart function. Exercised animals maintained normal growth rate, and cardiac hypertrophy was not present. Left ventricular RNA, DNA, and cytochrome c levels were unchanged. Heart functional measurements obtained in situ were similar in sedentary and exercised animals under control conditions. When subjected to sustained (1-3 days) aortic constriction pressure overload, exercised animals maintained or increased myocardial contractility. Contractility was depressed in sedentary animals. Both sedentary and exercised animals increased left ventricular end-diastolic pressure without changing contractility during acute (1-3 min) pressure overload. However, exercised animals were able to fully regain normal cardiac output when the acute overload was relieved. Cardiac output remained approximately 10% below control in sedentary animals. The improved ability of previously exercised animals to withstand pressure overload appears to be due to alterations in adaptation rather than preliminary augmentation of metabolism or function.

DNA; RNA; (dP/dt)/P; contractility; cytochrome c; stroke volume; cardiac output; aortic constriction; left ventricular end-diastolic pressure

Physical exercise is thought to have a beneficial effect on the overall cardiovascular system based on human epidemiological (9) and experimental (21) studies. Investigations in both the intact rat heart (7) and the isolated perfused rat heart (20) have also suggested that myocardial performance is improved following exercise training. The direct effects of exercise on myocardial performance have been difficult to determine from the above studies, since cardiac hypertrophy was considered to be present in the exercised animals. However, marked alterations in normal growth rate have been observed when adult male rats are subjected to exercise training (17, 18), which complicates the assessment of cardiac hypertrophy when a heart weight-body weight ratio is used for this purpose. Furthermore, forced swimming was utilized for exercise training in the studies of Crews and Aldinger (7) and Penpargkul and Scheuer (20) which, in itself, may impose neurogenic and hypoxic influences on the animal.

The studies of Oscai et al. (18) indicate that female rats maintain a normal growth rate when subjected to swimming exercise. Therefore, it seemed likely that by employing treadmill running with female rats, body weights comparable to unexercised animals could be maintained while avoiding the possible extraneous influence of forced swimming. In this way, the effects of exercise with respect to both the development of cardiac hypertrophy and myocardial function could be more appropriately evaluated. In addition, we examined the heart functional responses of exercised and sedentary animals during both acute and sustained increases in left ventricular afterload to determine whether previous repetitive exercise exerted a beneficial effect on the ability of the heart to withstand pressure overload stress.

Methods

Animal selection and exercise program. Female Sprague-Dawley rats weighing 90-110 g were initially screened to select animals willing to run on a motor-driven treadmill. Animals which met this criterion were assigned to either sedentary or exercise groups. Exercise animals were subjected to an 8-wk treadmill running program. Throughout the exercise program, the treadmill was maintained at a 5-deg incline and animals were exercised 5 days/wk. During the 1st wk, exercise animals ran twice daily at 19 m/min for 10 min. The running speed and duration were progressively increased until, during the 6th wk, animals were running once daily at 25 m/min for 60 min. During the last 2 wk of exercise, the running speed and duration were maintained at the 6th-wk level, but 1-min sprints at 35 m/min were interposed every 10 min throughout the exercise session. Sedentary animals received only normal cage activity. Both exercise and sedentary groups were weighed at weekly intervals to determine the effect of treadmill running on the growth rate of female rats.

Functional evaluation of intact heart. Animals were anesthetized with sodium pentobarbital (50 mg/kg, ip), and positive-pressure respiration with room air was initiated via a tracheostomy using a Harvard Apparatus rodent respirator. Either midline or intercostal thoracotomy was performed, and left ventricular pressure was measured by puncturing the ventricle with a 3.8-cm 22-
The left ventricular pressure pulse was recorded with high amplification to measure left ventricular end-diastolic pressure (LVEDP). The first derivative of left ventricular pressure (dP/dt) was derived using a resistance-capacitance differentiating circuit (Electrons for Medicine, model RC-1). This differentiator has a rated time constant of 0.5 ms, and amplitude is a linear function of frequency to 75 Hz. In some experiments, an electromagnetic flow probe (Carolina Medical Electronics, model 400) was placed on the ascending aorta. Flow calibrations were made in vitro with a short section of rat aorta, and flow measurements were corrected for hematocrit. All pressure and flow signals were recorded on an Electronics for Medicine DR12 photographic recorder.

With the DR12 recorder in the loop mode, left ventricular pressure derivative-left ventricular pressure loop plots were recorded (1). Each loop plot was composed of points taken at 2-ms intervals throughout a complete cardiac cycle. The slope of the linear isovolumic contraction portion of the loop was utilized to calculate a myocardial contractility index, (dP/dt)P⁻¹, by averaging values from at least three beats. Preliminary experiments with the intact rat heart preparation have shown that the contractility index used in the present studies is independent of increased heart rate, increased afterload, and decreased preload. Appropriate changes in the contractility index were observed with pharmacological agents known to influence the contractile state of the myocardium. The intact rat heart preparation remains functionally stable and within physiological blood gas and pH limits for at least 30 min following required surgical procedures.

Sustained pressure overload experiments. In two separate experiments, sedentary and exercise animals were assigned into two groups for subsequent study. Groups designated control received no experimental intervention other than functional evaluation of the intact heart. The remaining groups were subjected to left ventricular pressure overload produced by constricting the ascending aorta with a silver band as previously described (16). This procedure constricts the aorta to approximately 30% of its original cross-sectional area and results in a 30- to 40-mmHg left ventricular-aortic pressure gradient. Aortic constricted animals were studied either 1 or 3 days following surgery.

The position of the silver band used for aortic constriction prevented proper flow-probe placement; therefore, no flow measurements were taken from animals in the aortic constriction experiments. A left intercostal thoracotomy was used to expose the heart. After functional measurements had been taken in control sedentary and exercise animals, the heart was rapidly excised, separated into right ventricular and left ventricular (including septum) portions, and weighed. Left ventricular samples were subsequently analyzed for RNA (8), DNA (5), and cytochrome c (2) levels. Gastrocnemius muscles were also taken from sedentary and exercise animals in the control groups for cytochrome c analysis.

Acute pressure overload experiments. In a separate group of sedentary and exercise animals, the heart functional responses to acute pressure overload were determined. Animals were surgically prepared (midline thoracotomy with flow probe) as described above, with the exceptions that a ligature snare was positioned between the flow probe and the innominate artery and an abdominal aortic catheter was introduced to monitor aortic pressure. After control functional measurements had been recorded, the ligature snare was tightened to produce a 30- to 40-mmHg left ventricular-aortic pressure gradient which approximates the degree of pressure overload obtained from aortic banding. Measurements were recorded 1 and 3 min after the pressure gradient had been applied. The ligature snare was then released, and measurements were recorded after allowing 5 min recovery from the acute pressure overload. Following the final functional measurements, an arterial blood sample was taken from the abdominal aortic catheter for hematocrit determination. The heart was excised, separated into right and left ventricular portions, and weighed. Chemical analyses were not performed on these heart samples.

Statistical analysis. The Student t test was used to statistically analyze the data. Within groups, comparisons were made versus control values. Comparisons were also made between sedentary and exercise groups for any given experimental condition. A P value of 0.05 or less was considered statistically significant.

RESULTS

The treadmill exercise program employed in the present studies did not disrupt the normal growth rate of female rats as shown in Fig. 1. Therefore, the effects of exercise in producing cardiac hypertrophy could be assessed without resorting to body weight normalizing procedures. Exercise had no effect on either right or left ventricular weights (Table 1), and it may be concluded that cardiac hypertrophy was not present in exercised animals. The left ventricle of exercised animals did not show significant differences in RNA, DNA, or cytochrome c levels as shown in Table 1. In addition, cytochrome c levels were unchanged in gastrocnemius muscle of exercised animals (Table 1).

Although functional measurements obtained from sedentary and exercised animals were similar under control conditions, marked qualitative and quantitative differences were apparent following sustained pressure overload (Fig. 2). Similar degrees of pressure overload were produced in both groups of animals, as evidenced by left ventricular systolic pressure measurements. Both groups exhibited a significant increase in heart rate 1 day after aortic constriction. Heart rate remained elevated at 3 days; however, this increase was not statistically significant. Exercised animals did not show any significant increase in LVEDP either 1 or 3 days after aortic constriction. In contrast, LVEDP was significantly elevated in sedentary animals 1 day after banding and remained elevated at 3 days. The contractility index increased significantly in exercised animals 1 day after aortic constriction and then returned to normal.
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FIG. 1. Weekly body weights of sedentary and exercised animals during exercise program. Number of animals at each point is given in parentheses.

TABLE 1. Body weight, heart weight, and chemical measurements obtained from sedentary and exercised animals used in sustained pressure overload experiments

<table>
<thead>
<tr>
<th></th>
<th>Sedentary (15)</th>
<th>Exercise (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt, g</td>
<td>234 ± 2</td>
<td>236 ± 2</td>
</tr>
<tr>
<td>RV wt, mg</td>
<td>150 ± 3</td>
<td>158 ± 7</td>
</tr>
<tr>
<td>LV wt, mg</td>
<td>618 ± 9</td>
<td>607 ± 4</td>
</tr>
<tr>
<td>LV RNA, mg/g</td>
<td>2.53 ± 0.04</td>
<td>2.54 ± 0.04</td>
</tr>
<tr>
<td>LV DNA, mg/g</td>
<td>2.83 ± 0.04</td>
<td>2.76 ± 0.04</td>
</tr>
<tr>
<td>LV cytochrome c, mmol/g</td>
<td>4.0 ± 0.4</td>
<td>40.7 ± 0.5</td>
</tr>
<tr>
<td>Gastrocnemius, cytochrome c, mmol/g</td>
<td>9.5 ± 0.2</td>
<td>9.6 ± 0.2</td>
</tr>
</tbody>
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Values are means ± SE. The numbers of animals are given in parentheses. RV, right ventricle; LV, left ventricle.

levels. Sedentary animals exhibited a nonsignificant reduction in the contractility index 1 day after aortic constriction, and the index continued to decline, reaching significant levels at 3 days. These results indicate that although there were no differences in heart weight, selected indices of myocardial chemical composition, or heart function under control conditions between sedentary and exercised animals, previous exposure to repetitive exercise had influenced the myocardial functional responses used in meeting a sustained pressure overload. It could not be determined from these experiments whether functional differences were present immediately in response to pressure overload challenge or whether these differences represent a time-dependent adaptation. The acute pressure overload experiments were utilized to distinguish between these two possibilities.

As was the case with animals used for sustained pressure overload experiments, the exercise program had no significant effect on the body weight or heart weight of animals used for acute pressure overload experiments (data not shown). Control functional measurements were not significantly different in exercised and sedentary animals (Table 2). It should be noted that differences in heart rate, left ventricular systolic pressure, LVEDP, and the contractility index are apparent between control functional measurements in acute pressure overload experiments and control functional measurements in sustained pressure overload experiments.

These differences may be due to the flow probe placed on the ascending aorta and/or the fact that different thoracotomy procedures were employed. Nevertheless, control measurements were comparable in sedentary and exercised animals under both conditions.

The qualitative responses of both exercised and sedentary animals to an acute increase in afterload were similar at the time periods studied (Fig. 3). LVEDP was elevated while cardiac output and stroke volume were decreased. Heart rate and the myocardial contractility index remained essentially unchanged. These results indicate that the qualitative functional response to acute pressure overload was not influenced by previous exposure to repetitive exercise. The larger increase in LVEDP observed in exercised animals suggests that quantitative differences may be present; however, there was no evidence that exercised animals preferentially

![Graph showing body weights of sedentary and exercised animals during exercise program.](http://ajplegacy.physiology.org/)
utilized increased myocardial contractility in meeting acute pressure overload challenge. Therefore, the different myocardial functional responses observed during sustained pressure overload may represent some alteration in adaptive mechanisms. One indication for such a conclusion can be seen in the recovery response from acute pressure overload as shown in Fig. 3. When the pressure gradient was relieved, exercised animals were able to fully regain normal cardiac output in spite of a reduction in heart rate by increasing stroke volume above control levels. In contrast, both cardiac output and stroke volume remained approximately 10% below control values in sedentary animals following release of the acute pressure overload. The different recovery responses cannot be accounted for by differences in the degree of acute pressure loading, since left ventricular systolic pressure was increased to nearly identical levels. Both exercised and sedentary animals exhibited increased LVEDP without changes in the myocardial contractility index when challenged by acute pressure overload. In fact, exercised animals were able to maintain or increase the contractile state of the myocardium in the face of pressure overload challenge. The divergent contractility index responses seen in pressure overloaded hearts of exercised and sedentary rats suggest that the adaptive differences are mediated at the level of the contractile proteins. Increased myocardial failure, The latter possibility may be indicated by the depressed contractility index in these pressure-overloaded hearts, although overt signs of myocardial failure were not present. A depressed contractility index in the intact in situ rat heart would appear to be a reliable indication of depressed cardiac muscle function. Exercised animals did not show any evidence of a reduced contractility index during sustained pressure overload. In fact, exercised animals were able to maintain or increase the contractile state of the myocardium in the face of pressure overload challenge. The divergent contractility index responses seen in pressure overloaded hearts of exercised and sedentary rats suggest that the adaptive differences are mediated at the level of the contractile proteins. Increased cardiac actomyosin (3) and myosin (26) ATPase activities have been observed in exercised rats and would have direct bearing on the present observations in view of the associated influence of contractile protein ATPase activity on the myocardial contractile state. Myofibrillar ATPase activity has been shown to be depressed in pressure-overloaded failing hearts (6), and the reduced enzymatic activity correlates with depressed cardiac muscle function (6, 15). Thus, the sedentary animals in the present studies appear to be responding in a predictable manner to sustained pressure overload, while previously exercised animals are responding "abnormally." It could be assumed that a preliminary increase in myofibrillar ATPase activity due to exercise would allow an increased myocardial contractile state to be utilized as a

**DISCUSSION**

In the present studies, female rats subjected to 8 wk of treadmill running were compared with comparable sedentary animals. The female rat is not able (or willing) to perform treadmill exercise of the intensity and duration used with male rats (19); thus, we were required to employ a treadmill exercise program of moderate intensity and duration. The moderate nature of the exercise program may account for the fact that neither increases in heart weight nor alterations in normal myocardial performance were observed in exercised animals. Nevertheless, the present studies appear to be responding in a predictable manner to sustained pressure overload challenge. The different contractility index responses seen in pressure overloaded hearts of exercised and sedentary rats suggest that the adaptive differences are mediated at the level of the contractile proteins. Increased cardiac actomyosin (3) and myosin (26) ATPase activities have been observed in exercised rats and would have direct bearing on the present observations in view of the associated influence of contractile protein ATPase activity on the myocardial contractile state. Myofibrillar ATPase activity has been shown to be depressed in pressure-overloaded failing hearts (6), and the reduced enzymatic activity correlates with depressed cardiac muscle function (6, 15). Thus, the sedentary animals in the present studies appear to be responding in a predictable manner to sustained pressure overload, while previously exercised animals are responding "abnormally." It could be assumed that a preliminary increase in myofibrillar ATPase activity due to exercise would allow an increased myocardial contractile state to be utilized as a

**FIG. 3.** Functional measurements obtained from sedentary and exercised animals in acute pressure overload experiments. Values shown are percent of control. Numbers of animals are given in parentheses.

- **HEART RATE**
- **LV PRESSURE**
- **LV END-DIASTOLIC PRESSURE**
- **CONTRACTILITY INDEX**
- **CARDIAC INDEX**
- **STROKE INDEX**
compensatory mechanism during sustained pressure overload and would account for the functional responses observed. However, augmented cardiac muscle function might also be expected in exercised animals in response to acute pressure overload if myofibrillar ATPase activity was previously enhanced. There was no evidence for this response in acute pressure overload experiments, since neither sedentary nor exercised animals increased the myocardial contractility index. In addition, the elevated cardiac actomyosin ATPase activity reported by Bhan and Scheuer (3) appears to be dependent on the total duration of exercise and was not present in animals subjected to swimming exercise for time periods comparable to those used in our studies. We recognize the danger in comparing swimming exercise with treadmill running, and the question of exercise-induced changes in cardiac contractile protein properties requires further investigation.

Since left ventricular RNA content was not elevated in exercised animals, it is unlikely that the adaptive response represents a preliminary increase in myocardial protein synthetic capacity, although Meerson (15) has proposed such a mechanism for animals previously exposed to treadmill running. Left ventricular cellularity was also unaltered as evidenced by a similar left ventricular DNA content in exercised and sedentary animals. Previous investigations involving both male (17, 19) and female (18) rats have not demonstrated either increased myocardial mitochondrial mass or mitochondrial respiratory capacity in response to extensive exercise training. The present results agree with the above observations, since left ventricular cytochrome c levels were unchanged due to exercise. Therefore, preliminary biochemical and metabolic adaptations of the above nature are not a plausible explanation for the observed difference in functional adaptation.

The possibility of peripheral adaptations and/or neural contributions to cardiac performance must be considered since our experiments were conducted in the intact animal. It has been shown that skeletal muscle mitochondrial mass and respiratory capacity can be increased when animals are exposed to treadmill running (11). However, the moderate exercise program used in our experiments did not increase gastrocnemius muscle cytochrome c levels. Furthermore, it seems unlikely that enhanced skeletal muscle aerobic capacity would account for an increased myocardial contractility index associated directly with cardiac muscle function.

Peripheral cardiovascular adaptation would offer an attractive explanation for the results observed in exercised animals following acute pressure overload. Improved venous tone would result in greater venous return to the heart, elevated LVEDP, greater stroke volume, and cardiac output. However, this mechanism alone cannot satisfactorily account for the responses observed during sustained pressure overload, since LVEDP was not elevated in exercised animals. It would appear that other time-dependent adaptations occur when exercised animals are exposed to sustained pressure overload stress. In this regard, direct or indirect neural contributions cannot be eliminated from consideration.

Moderate exercise may have induced changes in the regulation of coronary blood flow or blood flow distribution within the myocardium. Studies by Gamble et al. (10) have demonstrated that coronary blood flow per gram of left ventricular tissue is significantly reduced in rat left ventricles which were hypertrophied as the result of pressure overload. Furthermore, a recent study by Malik et al. (14) has shown that myocardial oxygen extraction is markedly elevated under resting conditions in the pressure overload-hypertrophied dog heart. Taken together these studies suggest that coronary blood flow becomes a limiting factor in pressure-overloaded hearts, which may result in impaired myocardial performance. Since exercise training has been shown to have some influence on the coronary vascular system (3, 24, 26), improved myocardial oxygen delivery mediated by changes in coronary blood flow should also be considered as a possible explanation for the adaptive responses observed in previously exercised animals during both acute and sustained pressure overloads.

It is clear from our results that repetitive exercise need not stimulate cardiac hypertrophy or produce detectable alterations in normal myocardial performance in order to exert a beneficial effect on the heart. Although several possible preliminary biochemical and metabolic adaptations were not present in exercised animals, our studies could not delineate any specific mechanism responsible for the improved ability of previously exercised animals to withstand myocardial pressure overload. The observed differences seem more likely to be attributable to alterations in factors related to adaptation rather than preliminary augmentation of normal resting metabolism or function.

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